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EXAMINER	
ART UNIT	PAPER NUMBER
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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
SUITE 600
WASHINGTON DC 20005

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12-30-96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-20 are pending in the application.
   Of the above, claims 8-20 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-7 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims 1-20 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

1. Applicant's election with traverse of Group I, claims 1-7, in Paper No. 11 is acknowledged.

The traversal of the restriction between Groups I and II is on the ground(s) that the search and examination of groups would not impose a "serious burden".

This is not found persuasive because as made of record in the previous office action, Groups I and II have acquired a separate status in the art because of their different classification.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the earlier filed application(s) in the first sentence of the specification (37 CFR 1.78).

The declaration claims priority to PCT/US95/03216, however the

specification does not refer to the priority application.

Sequence Rules 37 CFR 1.821-1.825

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Figure 3 discloses amino acid sequences for "TNFR2 human" and "consensus", which are not listed in the paper copy of the sequence listing.

4. The specification is objected to because it does not comply with 37 C.F.R. 1.821 (d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification wherever a reference is made to that sequence. See M.P.E.P. 2422.04.

The following references to sequences require a SEQ ID NO:

page 5, figure 1 legend(bottom paragraph); and, page 6, figure 2 legend, "present invention" and "human type 2 TNF receptor". It is suggested that the appropriate SEQ ID NO: submitted in response to the above paragraph of this office action be inserted as well.

Claim Rejections - 35 USC § 112

5. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the disclosed nucleic acids comprising the sequence encoding SEQ ID NO:2, the mouse homolog, and allelic variants, does not reasonably provide the full scope of enablement for the whole genus of variants or fragments of polynucelotides encoding SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5 encompass fragments and variants of the disclosed sequences for hybridization because of independent claims 1 and 3 recitation of "at least 70% identity" and "fragment". The specification fails to teach how to make and use all variant

fragments. Such fragments encompass a genus with a large number of species which are not reasonably expected to be functional. For example, in hybridization assays nucleic acids bind non-specifically to proteins and other nucleic acids and the usefulness of a hybridization probe is in discriminating between the non-specifically bound probe and the specific binding of the probe for the desired nucleic acid under optimal hybridization conditions. One skilled in the art do not use random hybridization conditions to detect the desired specific nucleic acids because under non-optimal hybridization conditions the specific desired nucleic acid hybridization to the probe cannot be discriminated from the non-specific binding to undesirable nucleic acids. Furthermore, hybridization with polynucleotides 70% identical to the disclosed polynucleotides is an unpredicatable art. Since size of the nucleic acid is one of the parameters that affect hybridization, the size of the fragment in relation to other parameters of hybridization is important for the usefulness of hybridization with fragments. Without further guidance concerning specific hybridization conditions, one skilled in the art could not determine which of the fragments would be useful under whole genus of hybridization conditions

available. No working example nor guidance is provided concerning the use of all the different possible fragments under any hybridization condition. One skilled in the art would predict that a majority of the fragments would not be a useful probe for hybridization without specific hybridization conditions to detect the desired nucleic acid. The experimentation necessary to use nucleic acids for hybridization under the whole genus of conditions is undue.

Claims 6 and 7 encompass DNAs encoding variants and fragments of SEQ ID NO:2 polypeptide because they refer to expressing the polypeptide and are dependent on claims 1 and 2 which encompass polynucleotide variants and fragments which are "capable of hybridizing to and is at least 70% identity" with DNA encoding SEQ ID NO:2. Furthermore, claims 6 and 7 encompass proteins encoded by different translation reading frames of the polynucleotide encoding SEQ ID NO:2 because the start site of polynucleotide reading frame of the polypeptide is not limited to the polynucleotide encoding SEQ ID NO:2 polypeptide in frame. Finally, claims 6 and 7 encompass a protein encoded by the complement of polynucleotide fragments and variants encoding SEQ ID NO:2. However, the specification does not teach how to use:

variants and fragments of SEQ ID NO:2 polypeptide, out of frame translation products, and proteins encoded by the complement of polynucleotide encoding SEQ ID NO:2. One skilled in the art would assume that a TNF-receptor like polypeptide may be comprised of an extracellular binding domain, a transmembrane domain, and an intracellular domain for signal transduction activities. However, the specification does not indicate the predicted secondary or tertiary structure based on the deduced primary amino acid sequence. Furthermore, the specification indicates unpredictability when referring to the polypeptide of the invention as a "putative TNF receptor"(page 4, second paragraph). However, the specification indicates that the TNF receptor of the present invention binds TNF-β just as strongly as the monoclonal antibody binds to TNF-β while the receptor also binds TNF-α two-thirds as strongly as the monoclonal antibody binds to TNF-α(page 19, bottom paragraph). In addition to the binding affinity, one skilled in the art would require some indication of the function of the receptor. Binding of the ligand for the receptor is not predictive of the what type of functional role the receptor plays in the cell. Without indication of function for the receptor, any determination of

binding of a ligand or antibody to the TNF receptor of the present invention merely detects the presence of the protein without function. Receptors bind ligand and activate the receptor via an interaction which requires the tertiary folding to be proper and even the most conservative nucleotide changes leads to non functional protein or drastically altered binding due to changes to the tertiary structure of the protein. Mutations also lead to improper folding and failure to place the protein to the plasma membrane of the cell. The state of the art is such that one skilled in the art cannot use the primary amino acid sequence of SEQ ID NO:2 polypeptide alone to predict the tertiary structure of SEQ ID NO:2 polypeptide which would be required to determine ligand binding, function, and proper folding of SEQ ID NO:2 polypeptide. No working example nor guidance are provided to indicate that a change in the ligand binding pocket for SEQ ID NO:2 polypeptide could bind a ligand. Thus, variants with 70% identity to polynucleotide encoding SEQ ID NO:2 do not encode a functional protein. Furthermore, proteins encoded out of the translational reading frame of polynucleotide of SEQ ID NO:1 are not functional because they encode protein with no relationship to the receptor. Since no limitation has

been placed on where the polynucleotide translation begins it can begin at any translational reading frame and each out of frame translation product is not functional. Finally, proteins encoded by the complement of the disclosed sequence as well as variants and fragments would encode a protein with no relationship to the receptor and are not functional. No working example or guidance is provided to use polypeptides without function. Thus, such variants and fragments encompass a genus with a large number of species which are not functional. In view of the extent and the unpredictability of the experimentation required to practice the invention as claimed, one skilled in the art could not make the invention without undue experimentation.

6. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A deposit of the ATCC Deposit No. 75899 is required to enable the invention of claim 3. This determination has been made because the claimed ATCC Deposit No. 75899 properties have

not been fully disclosed or the materials required to construct the claimed ATCC Deposit No. 75899 have not been shown to be publicly known and fully available. The specification does not teach how to make the ATCC Deposit No. 75899 on page 6(second paragraph), pages 35(last paragraph) through 38, and page 41(first paragraph), in a sufficient manner to practice the invention because one skilled in the art could not determine the exact materials necessary to construct the ATCC Deposit No. 75899. It would require undue experimentation to determine the exact materials necessary to construct the ATCC Deposit No. 75899. Without a publicly available deposit of the above polynucleotide, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. A suitable deposit for patent purposes is required. It should be noted that the specification (pages 10-11) does not state that the material was deposited under the terms of the Budapest Treaty.

If a deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his

or her signature, stating (a) that the deposit has been made under the terms of the Budapest Treaty; and (b) that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then the requirements may be satisfied by an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or by a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and establishing that the following criteria have been met: (a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto; (b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; (c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited

material; (d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807 is provided; and (e) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function described in the manner in the specification.

In either case, the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification if it is not already present. See 37 C.F.R. §§ 1.803-1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being as being anticipated by Lewis et al.(Proc. Natl. Acad. Sci., 1991).

Lewis et al. disclose the cloning of the mouse tumor

necrosis factor receptor cDNA and the deduced amino acid sequence (page 2031, left column, Results; page 2832, figure1). Figure 2 (and page 2831, right column, Expression...) discloses the transfection of TSA21 cells with an expression vector comprising the cDNA and the expression of the TNF receptor protein which binds TNF with high affinity. Figure 4(page 2833) discloses the hybridization with TNF receptor nucleic acid probe in an mRNA northern blot.

Claims 1-7 encompass nucleic acids comprising a polynucleotide fragment that is capable of hybridizing to and at least 70% identical to polynucleotide encoding SEQ ID NO:2. Furthermore, claim 3 encompass nucleic acids comprising a polynucleotide fragment that is capable of hybridizing to and at least 70% identical to polynucleotide encoding SEQ ID NO:2 because the ATCC Deposit No. 75899 comprises a polynucleotide encoding SEQ ID NO:2. The polynucleotide enconding the TNF receptor of the present invention (SEQ ID NO:1) has 100% identity with the referenced TNF receptor between the nucleotide sequence 260-270 of the TNF receptor of the present invention SEQ ID NO:1 and the reference TNF receptor nucleic acid sequence of 178-188 (see attached sequence comparison). The mRNA northern blot

method uses the cDNA probe for hybridization.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Pak whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael D. Pak
1812
27 January 1997

DAVID L. FITZGERALD
PRIMARY EXAMINER
GROUP 1800

Application No. 08/469,637
Attachment/Paper No: 12

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☒ 7.
Other: INCOMPLETE CRF & PAPERCOPY - SEE ACTION FOR DETAILS

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.